

REMARKS

The March 25, 2009 Official Action has been carefully considered. In view of the present amendment and the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset, it is noted that a shortened statutory response period of three (3) months was set in the March 25, 2009 Official Action. Accordingly, the initial response period is due to expire June 25, 2009. This amendment and request for reconsideration is being filed before the expiration of the initial response period.

In the March 25, 2009 Official Action, claims 1-4, 33, 34, 44-47, 51, 52, and 55-62, stand rejected under 35 USC §103 as allegedly unpatentable over the combined disclosures of Kotze et al. (J. Controlled Release, 51: 35-46 (1998)), which is already of record (hereinafter "Kotze"), and Schipper et al. (Pharm. Res., 14: 923-29 (1997))(hereinafter "Schipper").

Kotze reports on the results of a study in which the effects of N-trimethyl chitosan chloride (TMC) on the permeability of intestinal epithelial cells (Caco-2 cell monolayers) was investigated and compared with those of chitosan hydrochloride and chitosan glutamate. The authors conclude that the charge, charge density and structural features of chitosan and chitosan derivatives are important factors determining their potential use as absorption enhancers for drugs absorbed by the so-called paracellular transport pathway, e.g., peptides and peptidomimetics agents.

Schipper is relied on for its disclosure that the degree of acetylation (DA) and the molecular weight of chitosans determine their absorption enhancing and cytotoxic properties. The examiner further relies on Schipper's disclosure that chitosans with a low DA (1 to 15%) promote drug absorption at both low and high molecular weights, while showing a clear dose-dependent toxicity, whereas chitosans with Das of 35 to 49% only increase the

absorption of drugs with high molecular weights, and display low toxicity. Based on these disclosures, the examiner asserts that absorption enhancement properties and toxicity may be controlled by selecting a chitosan with the optimal chemical composition (DA) and molecular weight.

Based on the combined disclosures of Kotze and Schipper, the examiner contends, at page 5 of the March 25 Official Action, that differences in MW will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such MW is critical. "Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation" [citation omitted]. This rejection is the sole ground set forth in the March 25 Official Action for refusing the present application.

In accordance with the present amendment, the substituent represented by X in the structural formula of claim 1 is further characterized as "hydrophobic." Support for this amendment is provided by the present specification, at page 7, line 1, and by original claim 23.

No new matter has been introduced into this application by reason of the present amendment, entry of which is respectfully requested.

For the reasons given below, the 35 USC §103 rejection of claims 1-4, 33, 34, 44-47, 51, 52, and 55-62, based on the combined disclosures of Kotze and Schipper is clearly improper in the first instance, and cannot be maintained with respect to the recently amended claims. This ground of rejection is, therefore, respectfully traversed.

**A. THE IMPROPRIETY OF THE 35 U.S.C. §103(a) REJECTION OF CLAIMS
1-4, 33, 34, 44-47, 51, 52 AND 55-62 AS ALLEGEDLY UNPATENTABLE
OVER THE COMBINED DISCLOSURE OF KOTZE AND SCHIPPER**

A rejection under 35 U.S.C. §103 is proper only when the claimed invention as a whole is shown to be obvious in view of the prior art. Thus, all claim recitations must be considered in determining obviousness over the prior art. *In re Boe*, 184 USPQ 38 (CCPA 1974). Moreover, since chemical compounds and compositions are inseparable from their properties, the properties of a claimed compounds or composition must also be considered as part of the “invention as a whole” when assessing patentability under 35 U.S.C. §103. *In re Albrecht*, 185 USPQ 585 (CCPA 1975).

It is well-settled that the examiner has the initial burden of establishing a *prima facie* case of obviousness under 35 USC §103. *Ex parte Walters*, 214 USPQ 735 (Bd. Apps. 1979). Furthermore, when a new compound or composition is alleged to be obvious based on a combination of prior art references, there must be an apparent reason to modify compositions of the prior art in the fashion set forth in the claims in question. *Ex parte Whalen*, 89 USPQ2d 2008 (BPAI 2008), citing *KSR International Co. v. Teleflex, Inc.*, 82 USPQ2d 1385 (2007).

In the present case, the 35 USC §103 rejection of claims 1-4, 33, 34, 44-47, 51, 52, and 55-62 based on the combined disclosures of Kotze and Schipper is improper because it clearly lacks the factual basis required to support the legal conclusion that the subject matter of the rejected claims, as a whole, would have been *prima facie* obvious.

Applicants’ invention relates to novel carbohydrate polymers having hydrophobic and hydrophilic side-groups that are effective for solubilising, *inter alia*, hydrophobic drugs. The invention cannot reasonably be considered *prima facie* obvious over the combination of

Kotze and Schipper, as neither of these two references discloses or suggest a solubilizing carbohydrate polymer having the substitution pattern called for in the formula in claim 1. Kotze discloses N-trimethyl chitosan chloride, which does not have any of the units m, n or p, given that the groups which would correspond to R', R'' and R''' are hydrogen in N-trimethyl chitosan chloride. The claims do not encompass hydrogen within the scope of these groups. Furthermore, even if hydrogen ever encompassed within the scope of R', R'' and R''', Kotze still fails to provide evidence of obviousness because N-trimethyl chitosan chloride does not contain the m unit in the claims, the group represented by X being absent from N-trimethyl chitosan chloride.

Similarly, with regard to Schipper, this reference does not disclose a compound having the formula set forth in the claims, since in the chitosans disclosed in Schipper, the groups represented by R', R'' R''' are hydrogen, which is not encompassed by the claims. Furthermore, even if hydrogen were encompassed, the compounds in Schipper do not have the n unit. If the Examiner views the N-acetyl group in the Schipper compounds as being equivalent to X in the formula in the claims, then applicants respectfully submit that the newly added recitation that X is hydrophobic further distinguishes over Schipper, since the short N-acetyl group in Schipper is not hydrophobic.

Thus, Kotze and Schipper considered either alone or in combination fail to disclose or suggest all of the structural features of the claims, and, therefore, cannot render the claims *prima facie* obvious.

There are other patentable differences between the presently claimed subject matter and the cited prior art references. Several notable distinctions with respect to Kotze are set forth in applicants' response to the proceeding Official Action, and are incorporated by reference herein. The main difference is that Kotze neither teaches nor suggests chitosans

which are suitable for solubilizing hydrophobic drugs. The primary distinctions over Schipper are summarized below.

Schipper, like Kotze, fails to teach or suggest chitosans that are effective for solubilising hydrophobic compounds. Notably, Schipper teaches that molecular weight and the degree of acetylation may be altered to yield chitosan compounds which increase the paracellular transport of hydrophilic drugs across Caco-2 cell monolayers. Furthermore, Schipper's examples are all hydrophilic polar compounds: mannitol, propidium iodide, hydrophilic dextran derivatives (FD-4 and FD-20), as can be seen, for instance, on page 923, column 1, lines 26-27; page 924, column 1, lines 40-46; page 926, column 2, lines 1-26 and page 928, column 1, lines 1-3; Table 1, Table 2, Table 3, Figure 3; and page 928, column 1, lines 12-17.

In combination, the teachings of Kotze and Schipper refer to the transport of hydrophilic compounds and make no mention of the use of chitosan together with compounds possessing the directly opposite fundamental physical property of low water solubility (i.e. hydrophobic compounds). The invention of a chitosan polymer for the delivery of hydrophobic compounds is not obvious from the teaching of chitosan polymers as delivery systems for hydrophilic compounds. Hydrophobic compounds in the presence of the polymers described by Schipper and Kotze would precipitate in the aqueous medium of the gut, and would not be transportable by the paracellular route. In actual fact, Kotze asserts that transport through the paracellular route is specifically for hydrophilic molecules (page 36, column 1, lines 45 – page 36, column 2, line 3). Schipper also asserts that the molecules disclosed therein enhance transport through the paracellular pathway (see, for instance, page 923, column 1, lines 35-38). The polymers of the present invention do not open tight junctions so as to act in this manner.

As stated by the Board in *Ex parte Whalen*, supra,:

[W]hen the prior art teaches away from the claimed [subject matter], obviousness cannot be proven merely by showing that a known composition could have been modified by routine experimentation or solely on the expectation of success; it must be shown that those of ordinary skill in the art would have had some apparent reason to modify the known composition in a way that would result in the claimed composition.

The examiner has failed to make such a showing in this case, and as a result, has not carried his initial burden of proof under §103.

It is also noteworthy that the molecular weight control of the presently claimed polymers primarily allows the polymers to be solubilised in liquids (higher molecular weights lead to the formation of gels). No mention is made of molecular weight affecting gelation by either Kotze or Schipper.

Although the foregoing remarks have been directed primarily at claim 1, claims 2-4, 33, 34, 44-47, 51, 52 and 55-62 depend directly or indirectly from claim 1. Any claim dependent from a non-obvious claim is also non-obvious. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988).

For all of the foregoing reasons, the §103(a) rejection of claims 1-4, 33, 34, 44-47, 51, 52 and 55-62 should be withdrawn upon reconsideration.

B. CONCLUSION

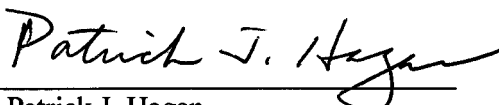
In summary, the claimed invention is based on the use of chitosan polymer derivatives to solubilize hydrophobic compounds, such as drugs. The characterization as being hydrophobic, as now recited in claim 1, further supports this utility. Neither of the cited

prior art references disclose polymers which have the substitution pattern called for in claim 1, and which are suitable for solubilizing hydrophobic drugs. These references clearly fail, therefore, to constitute evidence of unpatentability with respect to applicants' invention. Notwithstanding the examiner's assertion to the contrary, this is certainly not a case in which the general conditions of applicants' claims are disclosed in the prior art.

In view of the foregoing remarks, it is respectfully requested that the rejection set forth in the March 25, 2009 Official Action be withdrawn and that this application, as presently amended, be passed to issue and such action is earnestly solicited.

Respectfully submitted,

DANN DORFMAN HERRELL and SKILLMAN
Attorneys for Applicant

By 
Patrick J. Hagan
Registration No. 27,643

Customer Number 000110
(215) 563-4100 (telephone)
(215) 563-4044 (facsimile)
phagan@ddhs.com (email)